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NUTRITION REVIEWS

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NUTRITION REVIEWS

VOL. 6 OCTOBER, 1948 No. 10

NUTRITION PROGRAMS FOR INDUSTRIAL WORKERS

During World War II, all warring countries manifested concern over the supply of sufficient foods to industrial workers to permit and encourage production of war materials. Supplemental rations, through one device or another, were given to many workers, always with the principal objective of spending the minimum amounts of calories and of specific foods necessary to get the desired amounts of materials produced with as little labor unrest as possible. Nutritional requirements received much consideration, particularly in those countries where the total food supply was severely limited, but food habits, the morale values of particular foods, production priorities, agricultural policies, and other economic and social considerations generally weighed heavily in the determination of the amount and type of food supplied, as well as in deciding the method of distribution. In the United States, as in other countries, an elaborately organized educational program was undertaken. It was the hope of the nutritionists concerned with the program that, with some knowledge of food and nutrition and confidence in his country's food program, the worker could be persuaded to make the best use of available foods to protect his own health and diminish the force of some of the non-nutritional considerations involved in the determination of his country's food program.

No nutrition education program intended to improve the people's health is complete when it is directed solely to the consumer and when it is not accompanied by an active program to provide adequate amounts of the proper foods. The wartime nutrition program for industrial workers in the United States was set up to proceed simultaneously along the three lines indicated: education of the consumer, education of the food producer and supplier, and provision of foodstuffs. Perhaps the most successful and most widely known part of the program is that concerned with on-the-job or in-plant feeding. The War Food Administration endeavored to associate in-plant food services with nutrition education activities carried on within the plant; to educate managers and other food service workers about the proper purchase, storage, preparation, and service of foods; to encourage the concept of the in-plant food service as a desirable component of the plant's employee health and personnel program; and to obtain adequate amounts of rationed and unrationed foods to permit industrial food services to provide workers with decent meals.

No claim of an unqualified success is made for any part of this program, but that in-plant feeding did serve to meet a definite wartime need recognized by industry is apparent from the following facts: (1) In 1944, four out of every five war workers in manufacturing were in plants having food services (38.5 per cent of factory workers in war work actually obtained meals from in-plant facilities). (2) Between the fall of 1942 and the spring of 1945, the Industrial Feeding Programs Division of the War Food Administration, with a small staff of experts visiting plants on request only, gave individual technical assistance to two thousand, two hundred, and sixteen different establishments with approximately six million, seven hundred thousand employees. (3) "Industrial Nutrition Service," a monthly publication providing food and nutrition facts for the worker and his family and intended for use by editors of house organs, had a mailing list of four thousand, three hundred, and twelve (June 1945). (4) "Serving Many," a monthly service for food service managers containing information on food supply, nu-

trition, menu planning, and food purchasing, storage, and preparation, had a mailing list of one thousand, nine hundred, and seventy-five in June 1945, about one year after it was established. (5) Ten thousand copies of a booklet entitled "Industrial Feeding Management," published in April 1945, were distributed in response to requests. (6) One thousand, six hundred copies of the manual "Industrial Feeding Facilities" were requested by architects, engineers, food service equipment manufacturers, and other industrial and food service groups. (7) Approximately 64 per cent of all requests for technical assistance received by the Industrial Feeding Programs Division came from plant management, only about 26 per cent came from other federal and state governmental agencies, and the remaining 10 per cent came from labor, equipment companies, architects, and engineers. (For a more comprehensive account of the wartime industrial feeding program in the United States and of its accomplishments, the reader is referred to "Nutrition in Industry," 1946, International Labor Office, Washington Branch, 734 Jackson Place, Washington 6, D. C.)

During the summer of 1945, the federal government began to withdraw from the field of food and nutrition activities for workers, and in the spring of 1946 the Industrial Feeding Program Division (then in the Department of Agriculture) was terminated. The explanation of the federal government's withdrawal from this field as soon as possible after the end of the war lies in the objectives of the program accepted by top government administrators at the time of its authorization. It was thought of by these people as an aid to the production of war materials and as a means for obtaining the worker's cooperation in government war food programs. At no time did the policy makers of the Department of Agriculture or of the war production agencies seriously consider the industrial feeding and nutrition program as the basis for a long-term program to improve the worker's nutrition and health. Neither the expressed need of industry for continued assistance nor considerations of the worker's nutritional welfare had any bearing on the decision to terminate the program.

It must not be thought that all nutrition and food service activities for industrial workers ceased as soon as the federal government withdrew. In-plant feeding was a common practice in the United States before the war and there is good evidence that many industries which installed food services during the war are continuing to operate them. There has also been a remarkable change in the attitude of many industries toward their food services. Before the war such services were generally regarded merely as conveniences for the employees, now they are more commonly recognized to be a health measure having an important bearing upon employee morale and industrial efficiency.

Just how extensive in-plant feeding is at present is not possible to say. There has been no satisfactory survey since those made by the Industrial Feeding Program Division, War Food Administration, United States Department of Agriculture, in 1944 and 1945. The Committee on the Nutrition of Industrial Workers of the Food and Nutrition Board, National Research Council, hopes to be able to conduct a survey this year, designed to determine not only the extent of in-plant feeding but also the type and operation methods used, management methods, the extent of associated nutrition education, the interest taken by plant medical and personnel departments, the attitude of management, and the extent of employee participation.

The wartime food and nutrition program for workers was seriously handicapped by not having been provided with funds or personnel to permit it vigorously to promote or conduct research on nutritional requirements, educational technics, food habits, and efficient methods for the distribution, storage, preparation, and service of foods.

Reliable information of practical value in public health food and nutrition work is sorely needed on all of these items. Public health nutrition programs, such as those for industrial workers, will continue to be extremely vulnerable to political winds, to misinterpretations, and exploitation until more unassailable facts and effective methods are available with which to build.

This does not mean that education should cease until all of the relevant facts are known. It is the duty of the public health worker to utilize his judgment and that of other experts to develop and advocate the most effective health measures possible with the facts and methods at hand. It does mean that fundamental and applied research should be considered a major component of peacetime public health nutrition work. Certainly there is enough information to indicate that industrial workers and their families are among the less well nourished groups of the population and that special measures to improve their nutritional status are desirable.

A well conceived nutrition program, then, is directed to the food producer and supplier, as well as to the consumer, and contains a major element of research. In addition, programs for industrial workers should be set up with the primary intent of protecting and improving the health of the workers and this concept must be sold to industry, labor, the government, and all other groups and individuals concerned. Among the major objectives to be sought are an increase in the active life span of the worker; improvement in his health and resistance to noxious environmental factors; and improvement in his morale and efficiency on the job. For the most part these are long-term objectives, a fact which must be kept in mind by both the practicing nutritionist and the research worker. The performance of a worker on any particular task at any particular time may be affected by many factors other than his nutritional status, and too much reliance should not be placed on the results of short-term studies of work output in industry.

ROBERT S. GOODHART
The National Vitamin Foundation, Inc.
New York, N. Y.

FURTHER STUDIES ON VITAMIN B_{12}

The isolation by chemists of the Merck Research Laboratories of a red, crystalline compound from liver concentrates which is extremely active in the treatment of Addisonian pernicious anemia and in promoting growth of Lactobacillus lactis Dorner under defined conditions has been previously noted (*Nutrition Reviews* **6,** *245* (*1948*)). As so frequently happens in scientific investigation, parallel studies conducted elsewhere have yielded similar results.

E. L. Smith (*Nature* **161,** *638* (*1948*)) has reported results of fractionation procedures which resulted in isolation from proteolyzed ox liver of amorphous red materials which were highly active in pernicious anemia. In the preliminary phases, the fractions containing the curative substance were located entirely by clinical assay with human patients; subsequently, when it became evident that clinical activity could not be separated from red color, the fractionation was greatly expedited by following the color of various fractions. From four tons of liver, about 1 g. of highly active red materials was obtained. Electrophoretic examination revealed that this preparation was still impure, i.e., it contained several components, and subsequent fractionation of suitably treated concentrates has yielded a preparation with eight times the color intensity of the most active amorphous material. Clinical tests of the latter material have not been reported; the cruder amorphous preparations, how-

ever, were therapeutically active in single doses of 0.3 mg. It was noted that these preparations had approximately the color of cobalt salts; measurements made by the diffusion procedure indicated a molecular weight of about 3000 for the active principle.

In subsequent experiments, not described in detail, the crystalline antipernicious anemia vitamin was isolated from the amorphous preparations. Analysis of the crystalline material revealed the presence of cobalt and phosphorus in the ash (Smith, *Nature* **162,** *144 (1948)*), these elements being present in approximately the ratio of one atom of cobalt for three of phosphorus. The minimum molecular weight of the active compound calculated from its cobalt content is 1500 to 1600, a result in excellent agreement with those obtained by x-ray crystallographic study of the crystalline material.

The presence of cobalt and phosphorus in crystals of vitamin B_{12} has been reported also by the Merck group in a recent note (E. L. Rickes *et al.*, *Science* **108,** *134 (1948)*). As both groups of workers emphasize, discovery that this vitamin is a cobalt complex is a result of the highest significance. Anemias due to naturally-occurring dietary deficiencies of this element are met not infrequently in ruminants, though not in nonruminant animals (*Nutrition Reviews* **4,** *227 (1946)*; **6,** *141 (1948)*). It has sometimes been postulated that the effect of cobalt in ruminants is exerted indirectly through microorganisms of the rumen; perhaps the formation of vitamin B_{12} in the rumen will provide an explanation for the effectiveness of this trace element in such animals. However, cobalt also produces a marked hematologic effect in nonruminant animals, such as the rat, where its administration produces polycythemia. Further studies of the physiology and mode of action of vitamin B_{12} undoubtedly will further elucidate this interesting interrelation between an essential vitamin and an essential trace element in their respective relations to anemia.

The report by Smith (*loc. cit.*) from the Glaxo Laboratories states that their preparation had, in addition to hematopoietic activity, a favorable effect on subacute combined degeneration of the cord (combined system disease) in 3 patients who were studied. These clinical observations were made by C. C. Ungley but have not yet been published in detail. The English preparation of this antipernicious anemia substance was much less pure than the B_{12} isolated by the chemists at the Merck Laboratories. Hence, the favorable influence on this aspect of pernicious anemia might have been due to some fraction other than the vitamin B_{12}. Evidence bearing on this point is of theoretical and practical interest. If vitamin B_{12} serves to reverse the neurologic changes of combined system disease, it speaks for the singleness of origin of the hematologic and neurologic defects in PGA. Pteroylglutamic acid does not protect the subject with pernicious anemia from the development of the neurologic manifestations of combined system disease. If vitamin B_{12} exhibits both activities, this fact provides additional separation of the activities of pteroylglutamates and B_{12}.

L. Berk, D. Denny-Brown, M. Finland, and W. B. Castle (*New Engl. J. Med.* **239,** *328 (1948)*) report in detail on the effectiveness of vitamin B_{12} for a single case of the neurologic complication of pernicious anemia, combined system disease. The patient was a 41 year old mulatto known to have pernicious anemia. She had responded satisfactorily to purified liver extract six and four years previously. She became sensitive to various liver extracts and a relapse which occurred two years prior to the present admission had been treated with folic acid. The initial hematologic response to PGA was satisfactory, but the patient became inconstant in her medication and slowly developed a hematologic relapse. Simultaneously, she noted the appearance of a sense of pressure in the abdomen, unsteady gait, and transitory paresthesias. Physical examination revealed a pale, well nourished

woman with gross ataxia, positive Romberg's sign, and loss of position and vibratory sense in the lower extremities. Numbness and hypalgesia developed in the tips of the index and middle fingers. The erythrocyte count was 1.92 million.

This patient was placed on a diet free of meat, fish, and eggs and given 5 micrograms of vitamin B_{12} daily for ten days. A peak reticulocytosis of 16 per cent was observed on the sixth day of treatment and a steady increase in red cells was observed. By the tenth day of therapy there had been an appreciable increase in the red cell count and remarkable changes in the neurologic disorder. The paresthesias had disappeared. The plantor responses returned to normal, the patient's gait was much more steady, and she could walk unsupported. Vibratory sense began to return. After nine injections of the crystalline vitamin, therapy was discontinued for a week, during which time a beginning neurologic worsening was noted. Upon reinstitution of therapy, the neurologic signs and symptoms again abated. Thus, it would seem established that the crystalline vitamin B_{12} was responsible for the neurologic improvement which was observed in this patient.

This patient of Berk *et al.* had developed a constant sensitivity to liver extracts. No sensitivity reaction followed administration of vitamin B_{12}, indicating that the sensitivity to liver extract was due to some component other than vitamin B_{12}. Pteroylglutamic acid likewise does not produce allergic reactions in patients who have become sensitized to liver extract.

Confirmation of these two important observations will be awaited with unusual interest. The evidence to date indicates that the vitamin B_{12} is a more complete replacement agent in the treatment of pernicious anemia than is PGA. Studies over a long maintenance period are necessary to establish whether it alone will suffice to maintain in remission all aspects of the syndrome of pernicious anemia. Additional hematopoietic substances may yet be unidentified in active liver extracts.

DIET AND HYPERTENSION

For many years restrictive diets of many types and modifications have been used with variable results in the treatment of hypertension and certain kidney diseases. In recent years the "rice diet," instituted by W. Kempner in 1944 has had wide acclaim, both by the layman and the professional man. Since that time Kempner (*Am. J. Med.* **4,** *545 (1948)*) has studied a large number of patients maintained on this regimen and has reported his results to date in 500 patients with hypertensive cardiovascular disease.

Most of the patients were seriously ill and had failed to respond to other forms of treatment. Of the 500, 178 failed to improve, including 26 who died. The remaining 322 showed a decreased arterial blood pressure of 20 mm. of mercury or more, a reduction in heart size (x-ray), a reversion to a more normal electrocardiogram, or disappearance of severe retinopathy.

Kempner's rice diet is strict, consisting of from 250 to 350 g. dry weight of rice daily, cooked only with plain water or fruit juice, together with fruit, fruit juice (700 to 1000 ml. daily), and white sugar or dextrose in amounts of from 100 to 500 g. Salt in no form is allowed. Dates, nuts, avocados, and dried fruits are also eliminated. The diet is said to provide in 2000 calories 5 g. of fat or less, about 20 g. of protein, and not more than 200 mg. of chloride and 150 mg. of sodium. Vitamins are given as follows: vitamin A 5000 units, vitamin D 1000 units, thiamine 5 mg., riboflavin 5 mg., niacinamide 25 mg., and calcium pantothenate 2 mg. The diet is "continued without modification until those conditions which were an indica-

tion for its use have disappeared." Only then are small amounts of vegetables and lean meat allowed.

Weight reduction was common during the first few weeks of the diet. Presumably this was due in part to fluid loss, although caloric restriction may have contributed an unknown amount to the weight reduction. Studies of basal oxygen consumption are not reported. Such determinations might be helpful in estimating the degree of caloric restriction and subsequent weight loss.

Considering the very low protein intake, knowledge of the state of nitrogen balance observed in patients on the rice diet would be interesting. Such studies are not reported, although the author states that the protein equilibrium is maintained. This fact is arrived at by comparing the average total urinary nitrogen excretion in patients maintained on the rice diet, with the intake estimated to be 20 g. per day. Actual chemical determination of the total nitrogen intake and of both urine and stool nitrogen was not made, so that a true nitrogen balance cannot be constructed. There is evidence that polished rice will induce greater weight gain in animals than wheat flour fed at the same dietary protein level—5.8 per cent (B. Sure, *Proc. Soc. Exp. Biol. Med.* **61,** *342 (1946)*). Nevertheless it would be surprising to find consistent nitrogen equilibrium in man at a dietary level of as little as 20 g. of protein per day. This amount is less than the minimum for maintaining equilibrium estimated by F. J. Stare, D. M. Hegsted, and J. M. McKibbin (*Ann. Rev. Biochem.* **14,** *431 (1945)*), and by M. Bricker, H. H. Mitchell, and G. M. Kinsman (*J. Nutrition* **30,** *269 (1945)*).

Further evidence that the rice diet may not provide enough protein to insure nitrogen balance is presented by W. B. Schwartz and J. K. Merlis (*J. Clin. Invest.* **27,** *406 (1948)*). These investigators studied one patient with hypertension and 6 without, all maintained on the strict rice diet. Negative nitrogen balance was consistent in both, of 3.22 and 2.67 g. of nitrogen per day. It was further found that the nitrogen intake was 2.63 g. (16.5 g. of protein) rather than 3.28 (20 g. of protein) as Kempner estimated. The evidence to date seems pretty clear, therefore, that nitrogen equilibrium is not maintained with the rice diet. It is not surprising, therefore, that most of the patients who follow the diet strictly, lose weight. However, anemia and hypoproteinemia did not occur in any of the patients Kempner followed. How long this strict protein deficient diet can be kept up without overt signs of protein deficiency would seem to be a pertinent question.

Blood constituents, in certain of the patients, were found by Kempner to change following the rice diet. There was some decrease in the blood nonprotein nitrogen and urea concentrations. Blood cholesterol, initially above normal in 70 per cent of the patients, fell, although 4 patients with a low cholesterol concentration exhibited a rise to normal. The changes were about the same for both free and esterified cholesterol. Both sodium and chloride concentrations in the blood fell slightly, while potassium rose. Although these electrolyte changes were not great, Kempner found them to be statistically significant. Likewise, as might be expected, urine sodium and chloride fell to very low levels (in terms of grams per liter of urine). Urine potassium rose.

Since Kempner's introduction of the strict dietary regimen a number of studies along the same line have been made. A. Grollman *et al.* (*J. Am. Med. Assn.* **129,** *533 (1945)*) had some success in lowering blood pressure by simple but strict restriction of sodium intake. G. A. Perera and D. W. Blood (*J. Clin. Invest.* **26,** *1109 (1947)*) studied a group of patients with uncomplicated hypertension. Although rigid salt restriction reduced the blood pressure somewhat and added salt produced a slight rise, the effects were not marked. Their diets furnished from 1700 to 2200 calories daily and from 70 to 80 g. of protein. With this amount of protein, nitro-

gen equilibrium is assured unless the calories fall too low. In addition to the much higher protein intake than that used by Kempner, the diet used by Perera and Blood furnished about 250 to 350 mg. of sodium as compared with the value of 150 mg. given by Kempner. Whether these differences in diet account for the better results reported by Kempner cannot be stated, but it is clear that the two studies are not necessarily comparable.

H. A. Schroeder (*Am. J. Med.* **4,** *578 (1948)*) has reviewed his own studies with low sodium diets in hypertension and has analyzed the results of others. He emphasizes, as also do Perera and Blood, that to decide upon the relative importance of dietary sodium, care must be taken to provide control periods of sufficient length so that the only change is in the diet. Schroeder studied 6 patients with hypertension who had been in the hospital on control periods for about a month before instituting the Kempner rice diet. In 3 of the patients with severe hypertension no change occurred in the diastolic pressure at all, while in 2 a slight fall occurred. In only one patient did the pressure fall as much as 20 mm. of mercury. Schroeder has reviewed the recent but relatively unknown work of H. J. Viersma published in Amsterdam (see Schroeder, *loc. cit.*). In this study control periods were long, and the results were much the same as those found by Schroeder.

That there may be dangers from too rigid salt restriction in some patients is also pointed out by Schroeder. In instances of "salt losing nephritis" severe depletion of the blood in sodium and chloride may be induced with associated uremia and death.

M. E. Flipse and M. J. Flipse (*South. Med. J.* **40,** *721 (1947)*) studied as outpatients the effect of the Kempner rice diet on 32 patients with either essential hypertension or renal hypertension. They observed a beneficial effect upon the blood pressure of 20 of these patients, although because of the kind of patient strict control periods were not possible. Only 13 of the successful cases had a drop of 20 mm. of mercury or more, although in 4 the drop was 40 mm. or more. Weight loss of greater than 10 pounds occurred in only 7 of these patients and further, the degree of blood pressure fall was no more in those who lost weight than in those who did not.

There has been a considerable amount of speculation concerning the mechanism of action of the rice and other low sodium diets. Generally speaking, sodium has been implicated as the controlling factor. However, it is still unclear how sodium withdrawal affects the blood pressure. Moreover, it should be emphasized that not only is the Kempner diet low in sodium, but it is low in total calories, very low in fat, and as shown above, it is so low in protein that nitrogen equilibrium is difficult, if not impossible, to attain. The role of limiting these other factors in addition to sodium must be taken into account in interpreting the therapeutic results, and in understanding the mechanism of action.

Another recent contribution to the subject of diet and hypertension is the report of J. Brozek, C. B. Chapman, and A. Keys (*J. Am. Med. Assn.* **137,** *1569 (1948)*). The authors discuss the results of two studies: first, the controlled one of the authors on individuals with normal blood pressure, and secondly, the mass starvation experiment unwillingly carried out during the siege of Leningrad.

In the first study, 36 normal young men were subjected to semistarvation for six months. Various cardiovascular measurements were followed through this phase and during the subsequent period of rehabilitation as well. During the period of dietary restriction the daily food intake furnished 1600 calories with 49 g. of protein. The intake of sodium was not known, but it was unrestricted. There was a definite but not pronounced fall in the mean arterial blood pressures (from 105 to 93 and 70 to 63, systolic and diastolic, respectively). This was paralleled by a fall in venous pressure, rest-

ing pulse rate (to as low as 37 per minute), basal oxygen consumption and, of course, of body weight. Roentgenographically the heart size decreased.

During rehabilitation there was a gradual change in these measurements to normal. Although hypertension was not observed during rehabilitation, moderate dyspnea and tachycardia on exertion occurred, particularly when the increase in food intake was marked. It was thought that there was a considerable strain on the cardiovascular system in these men, which was borne out by the experience of one man whose food intake during rehabilitation furnished from 7000 to 10,000 calories daily. In his case a recurrence of edema was observed after two weeks of this diet and dyspnea on exertion was evident. The heart size was found to have increased and the venous pressure rose to 20 cm. of water.

The second study covering the years during and following the famine in Leningrad was published in Russia (Leningrad: Medgiz. *p. 155 (1945); Ibid. p. 186 (1946)*) and the results are discussed by the Minnesota authors. During the period of semistarvation, emaciation, weakness, bradycardia, and decrease in blood pressure were observed. There was also a reduction in the incidence of hypertension and symptoms usually related thereto. Angina pectoris and myocardial infarction likewise were reduced in incidence.

Soon after the siege of Leningrad was over and refeeding was begun, hypertension reappeared and became a major medical problem. In one study approximately 10,000 "normal" persons were examined and the percentage with elevated blood pressure (above 140 mm. systolic and 90 mm. diastolic) was compared with a similar prewar survey (1940). In the age group 30 to 39, for example, the prewar incidence of hypertension was 7 per cent, while it was 30 per cent during refeeding. The increase in the age group 40 to 49 years was from 25 to 50 per cent. The increased incidence was thought not to be due to changes in the age and sex distribution of the population. Concomitantly, there was approximately five times increase over prewar in the hospital admissions for hypertensive disease, which had dropped markedly during the famine. In June, 1943, 60 per cent of all hospital admissions were for hypertensive disease. Symptoms such as headache, vertigo, and syncope became much more prominent than before the war, as were retinal hemorrhages and exudate. The increased incidence of congestive failure in hypertensive patients also was alarming, while renal damage not only did not increase but probably actually decreased in incidence.

Unfortunately, no knowledge of the salt intake was available for Leningrad, although the authors thought it to be low but not as meager as required by Kempner.

There is no doubt from these various studies that restricting the diet produces dramatic changes in cardiovascular function. Equally startling are the reverse changes with epidemic hypertensive disease following refeeding as observed in Leningrad. Unquestionably the role of food in the pathogenesis and therapy of hypertensive disease deserves careful investigation.

ATYPICAL INTESTINAL OBSTRUCTION POSSIBLY CAUSED BY NUTRITIONAL DEFICIENCY

D. J. Leithauser (*Surg. Gynec. Obst.* **86,** *543 (1948)*) described 6 patients with intestinal obstruction with severe abdominal distention which he attributes to nutritional deficiency, more specifically to thiamine deficiency.

Because one patient complained of a sore mouth, attention was directed to the possi-

bility of nutritional deficiency and specific questions brought to light a history of chronic alcoholism. In this instance the intestinal symptoms and the radiologic findings led to a preoperative diagnosis of annular carcinoma of the sigmoid. No such lesion was found at operation and postoperatively the abdominal distention increased. When vitamin therapy was instituted the distention disappeared.

The second patient, also an alcoholic, was subjected to operation for "acute appendicitis" but there was so much intestinal distention that the appendix was not readily accessible and was not removed. When uncontrollable distention continued after the operation the experience in the first case was recalled and vitamin therapy was instituted and was followed by equally striking results.

Review of 2 earlier cases of severe adynamic ileus of the same type revealed that these patients had also been alcoholics. In one, operation was performed because of a mistaken diagnosis of acute appendicitis, but no pathologic evidence was found in the appendix to account for the symptoms. The intestinal obstruction after operation progressed with severe alcoholic delirium to a fatal outcome. The fourth patient had developed severe distention after an operation for inguinal hernia, but this patient recovered without administration of thiamine chloride.

Two patients were not alcoholics but had been on greatly restricted diets, in one instance for gallbladder disease and in the other for weight reduction. In these cases no operation was performed since nutritional deficiency was suspected as the cause of the distention. The administration of thiamine chloride and vitamin B-complex was associated with striking and complete relief of the symptoms.

These observations are of interest, though it must be stressed that no really satisfactory evidence is offered to prove that the distention observed was actually due to nutritional deficiency. Certainly the conclusion that the deficiency was specifically due to lack of thiamine cannot be accepted since the patients received vitamin B-complex and protein in addition to thiamine. Nevertheless it should be pointed out that there is experimental evidence to indicate that intestinal disturbances may be associated with or may result from nutritional deficiency. R. Golden (*J. Am. Med. Assn.* **117,** *913 (1941)*), among others, has described a "deficiency pattern" of the small intestine discoverable on radiologic examination. Again, J. S. Brown and H. C. Trowell (*Lancet* **II,** *812 (1944)*) reported a syndrome in Polish refugees and in African and Indian adults and children in which the roentgenologic picture was similar to that described by Golden, and the symptoms were suggestive of pyloric obstruction. In their cases great gaseous distention of the colon was common. More specifically, it has been observed that in thiamine deficiency in the pig (M. M. Wintrobe *et al.*, *Bull. Johns Hopkins Hosp.* **71,** *141 (1942)*) abdominal distention is one of the most striking early manifestations. Thus, while the evidence offered by Leithauser is not convincing it must be admitted that there is some basis for his suspicions, and that his advice that a nutritional disturbance be suspected in any case in which the digestive symptoms, clinical, and radiologic findings seem atypical or anomalous, is without harm. Furthermore, his own practice of administering parenterally vitamin B-complex with high thiamine content to all surgical patients the day before operation and daily for three days thereafter would seem to be a harmless and perhaps occasionally a beneficial procedure.

LIPOTROPIC SUBSTANCES IN CIRRHOSIS OF THE LIVER

The effects of protein, choline and cystine, and of methionine in the prevention and cure of fatty and in some instances cirrhotic changes in the liver of experimental animals are well established. The use of these substances in human liver disease has been recommended, but the results to date have been either equivocal or have failed to demonstrate clearcut improvement (*Nutrition Reviews* **4,** *27, 180 (1946)*). The effect of these "lipotropic" substances in cirrhosis of the liver is particularly difficult to interpret because of the well known unpredictability of the course of this disease. F. Steigmann (*J. Am. Med. Assn.* **137,** *239 (1948)*) found the use of lipotropic substances together with a diet high in protein, carbohydrate, and vitamins and low in fat to be "efficacious."

Two hundred and forty-seven cases of cirrhosis of the liver were studied on four regimens during a ten year period. During the years from 1937 to 1940, 81 patients were treated with a diet high in carbohydrates, but low in both fat and protein. The second and third groups were treated from 1941 to 1947 with a high protein and high vitamin but low fat diet, the protein of which was "lactovegetarian" in the second group of 78 patients, and supplied as meat in the third group of 41 patients. The 43 patients in the final group were given lipotropic substances in addition to the high meat protein diet. Twenty-five patients were given cystine and choline (3 g. daily), 12 patients were given 3 g. daily of choline alone, and 10 patients were given 3 to 5 g. of methionine daily.

The results are presented as morbidity and mortality rates. During the initial hospitalization, the deaths were 50, 32, 44, and 13 per cent for the four groups of patients, respectively. The period of hospitalization averaged thirty-seven days for group 1, from one to one hundred and fifty days in groups 2 and 3, while no definite period is given for the fourth group, although it is stated that most received the lipotropic substances for at least four weeks. Thus, it might be supposed that few, if any, patients included in this group died within the first month. This was apparently not true of the other groups. There is no question that the mortality rate of the "treated" group was far better than that of the controls, but to assure validity of the mortality rate comparisons the cases falling into the two groups should, perhaps, have been selected by some more arbitrary method such as strict alternation. Moreover, because of the small size of the series and the variable and unpredictable nature of the disease, as many of the variables as possible should be analyzed.

The percentages of abnormal physical findings are presented for comparison of the second and third groups with those of the group receiving the lipotropic substances. Although the four physical findings given cannot define the character or severity of the liver disease, the two groups were fairly comparable for the findings listed.

Further analysis of the results was made for the repeat hospitalizations. However, the number of cases lost from the original series makes the groups so small that comparison rests on tenuous grounds. Moreover, the mortality rates between the four groups did not differ significantly. The authors then determined the over-all percentage of mortality for each of the groups, including together the mortality of both the first and subsequent admissions. Although the percentage of fatal results was lowest for the group treated with the lipotropic substances, the results are difficult to interpret, again because of the large proportion of the cases in all groups which were not followed.

Although the lipotropic substances were administered in an effort to hasten the removal of fat from the liver, other unspecified "beneficial" effects were observed. It was also noted by the authors that despite the

disappearance of fat as observed by liver biopsy, some patients failed to improve with the supplements.

In view of the complexities of the problem it might be suggested that investigators contemplating further studies of the effect of lipotropic substances in liver disease either alternate treated and control cases, or select some other statistically valid method of study.

NUTRITIONAL REQUIREMENTS IN PREGNANCY AND LACTATION

That nutritional requirements are increased during pregnancy and lactation has been known for years, but only recently have quantitative allowances of nutrients been set. Moreover, the results of malnutrition or of undernutrition during these periods of stress are serious enough to form an important public health problem which could be solved by proper education of physicians and laity. The evidence establishing the nutritional requirements during pregnancy and lactation has been summarized by B. S. Burke and H. C. Stuart (*J. Am. Med. Assn.* **137,** *119 (1948)*).

The evidence in human beings that nutrition is important in pregnancy is now clear-cut. Several studies have shown that mothers who consume an adequate diet during pregnancy have significantly fewer complications (especially toxemia), as well as fewer abortions, premature births, stillbirths, and neonatal deaths. In addition, these mothers have babies who are healthier, heavier, and slightly longer at birth than those of mothers subsisting on inadequate diets. These observations were borne out by the studies in famine stricken countries during World War II, except when the famine became severe enough to increase markedly the incidence of amenorrhea and reduce the birth rate.

The recommended daily allowances of nutrients during pregnancy and lactation are discussed in some detail by the authors who point out that although those advised by the Food and Nutrition Board of the National Research Council (*National Research Council, Reprint and Circular Series* **122** *(1945)*; *Nutrition Reviews* **3,** *287 (1945)*) are thought to be ample, they presuppose that pregnancy begins with the woman in good nutritional status. Since this is frequently not the case, the allowances may in some instances have to be increased.

Although the caloric requirements during pregnancy are extremely variable, the National Research Council has recommended a 20 per cent increase. However, the increased requirements for protein, minerals, and vitamins may be 100 per cent or more. As the authors make clear, increasing the intake of these nutrients without a concomitant caloric increase requires particular care in planning the diet.

The increased protein requirement during pregnancy represents not only the need of the fetus, but is accounted for also by storage of a considerable amount of protein in the maternal tissues. The evidence for this rests on nitrogen balance studies which the authors discuss. A considerable number of women have been found whose protein intake fell far below the optimum with definitely harmful effects on the fetus.

The requirements for calcium, phosphorus, and vitamin D are stressed particularly because so many women begin pregnancy with an apparent calcium deficiency. Milk is, of course, the most important source of calcium and phosphorus in the recommended diet.

The actual iron requirement during pregnancy stands on somewhat less firm ground than that for other nutrients. In fact, the anemia observed during pregnancy may in part be physiologic, due to increased plasma volume. The macrocytic anemia of pregnancy is not common in this country, but it responds readily to treatment with unrefined

liver extract (*Nutrition Reviews* **3,** *327 (1945)*) and probably to folic acid as well. There is evidence, however, that folic acid should not be used alone. When it is administered to patients with macrocytic anemia of pregnancy, it should be, just as in pernicious anemia, in conjunction with liver extract.

While the requirement for vitamin A during pregnancy is not known, an allowance of 6000 I.U. daily has been recommended and is best supplied, the authors suggest, by foods such as milk, butter, fortified margarine, liver, and leafy green and yellow vegetables. The actual requirements for the vitamin B-complex vitamins are not known, but good evidence places the allowances well above those for the nonpregnant woman. The allowance for ascorbic acid is likewise increased.

Good food is certainly the best way to supply these various nutrients. The authors outline a basic diet which includes daily a quart of milk, a liberal serving of lean meat, one egg, two or more servings of fruit and of vegetables, four slices of enriched or whole grain bread, two tablespoonfuls of butter or fortified margarine, and some form of vitamin D to supply 400 to 800 I.U.

In discussing the altered requirements during lactation, the authors note first that the caloric requirement may be increased 50 per cent above normal. Likewise, roughly 2 g. of protein per kilogram of body weight are recommended. The mineral and vitamin allowances are also increased, although in many instances little is known of the actual requirements. An additional pint of milk is recommended as well as "liberal" amounts of vegetables and fruits.

PYRIDOXINE AND SPECIFIC DYNAMIC ACTION

One of the characteristic results of feeding proteins or amino acids is a rise in oxygen consumption (heat output) over that exhibited by a control animal in a similar state of activity, a phenomenon referred to as "specific dynamic action." The magnitude of the effect varies from one amino acid to another. It has been postulated that the effect is due to the energy liberated during oxidative deamination of the amino acids, and it may be significant that those amino acids which show little or no specific dynamic action (for example, glutamic acid and aspartic acid) are those which are highly active in transamination systems.

Since it is now well known that pyridoxine enters into several metabolic reactions and conversions involving amino acids, including transamination (*Nutrition Reviews* **5,** *98 (1947)*), it was of interest to determine the effects of this vitamin on the specific dynamic action of amino acids. D. P. Sadhu and S. Brody (*Am. J. Physiol.* **151,** *342 (1947)*) have conducted experiments of this nature. Female rats (150 to 200 g. in weight) were fasted for twelve hours, then given the sodium salts of the amino acids (0.5 g. glutamic acid or tyrosine) with a blunt needle and record syringe and with or without added pyridoxine (5 mg.). The effects on oxygen consumption were then followed. In both cases a significant lowering of the specific dynamic action of the amino acids was observed when pyridoxine was administered with the amino acid, which lasted over the entire nine hours of observation. Administration of pyruvic acid with glutamic acid also greatly decreased the specific dynamic action of the amino acid.

Under conditions which should favor transamination, therefore (i.e., addition of pyridoxine and of pyruvic acid), the specific dynamic action of these amino acids is lowered. In separate trials whose protocols are not given, no such effect was observed with glycine, which does not undergo transamination. For these reasons, the

authors believe that those amino acids which are deaminated by transamination show little or no specific dynamic action, while those which are not deaminated by transamination, but presumably by oxidative deamination, show high specific dynamic action. Administration of pyridoxine or pyruvate decreases the specific dynamic action of the former group because it provides conditions permitting all of the deamination to go by way of the transamination reaction. The experimental observation that pyridoxine administration also lowered the specific dynamic action of glucose they explain on the basis that glucose will yield pyruvate on dissimilation, which acts as an amino group acceptor in transamination, the latter process being catalyzed by pyridoxine.

This investigation is illustrative of the growing and commendable efforts to explain over-all metabolic effects in intact animals in terms of isolated chemical systems. In the present instance, however, two objections to the proposed explanation have not been discussed. First, although the specific dynamic action of tyrosine was dramatically lowered by simultaneous administration of pyridoxine, tyrosine does not participate in any of the isolated transamination reactions so far investigated. It is possible, therefore, that the explanation is at fault in this instance, and that pyridoxine exerts its influence in some other fashion. Secondly, even though glutamic acid is deaminated via transamination with pyruvate, the alanine which is thus formed remains for disposal, eventually, presumably by some type of oxidative deamination. It is difficult to understand, on this basis, why the intermediary interpolation of the transamination reaction should be expected to lower the observed specific dynamic action.

RUTIN TREATMENT OF CAPILLARY FRAGILITY

A flavinoglucoside isolated in 1860 from the early blossoming leaves of the buckwheat plant is known as "rutin" (J. F. Couch, J. Naghski, and C. F. Krewson, *Science* **103,** *197* (*1946*)). Within the past few years several clinical reports have appeared concerning the possible therapeutic usefulness of this drug in daily doses of 60 to 180 mg.; even with these large doses no untoward effects have been noted in the human being. The compound has been reported of value in the treatment of increasing capillary fragility in cases of hypertension and in arresting hemorrhage in cases of hereditary telangiectasia (S. D. Kushlan, *Gastroenterology* **7,** *199* (*1946*)) and idiopathic pulmonary hemorrhage. Others, however, have noted no effect of rutin on increased capillary fragility (J. F. McManus and F. L. Landrigan, *Proc. Am. Fed. Clin. Res.* **3,** *51* (*1947*)).

Two critical studies have been reported concerning the effect of rutin on the capillary fragility and retinopathy of patients suffering from diabetes mellitus. In the first of these (L. M. Levitt, M. R. Cholst, R. S. King, and M. B. Handelsman, *Am. J. Med. Sci.* **215,** *130* (*1948*)) 12 diabetic patients with diabetic retinal hemorrhages and markedly increased capillary fragility were studied. The patients were saturated with ascorbic acid (100 mg. three times a day for one month) prior to treatment. They were then given rutin (20 mg. three times a day) for two months and the dose was increased to 40 mg. three times a day for another month. Five of the 12 patients were given ascorbic acid, 300 mg. daily, with rutin during the entire period of study. Capillary fragility was determined by the positive pressure test as modified by I. S. Wright and A. Lilienfeld (*Arch. Int. Med.* **57,** *241* (*1936*)). The hemorrhages in the retina had been charted by the ophthal-

mologists of the hospital staff; the disappearance of any retinal hemorrhage which had been charted previously was recorded as an improvement.

After treatment marked improvement in the fragility of the capillaries of the skin appeared in only 4 of the 12 patients; 2 of these 4 had hypertension; the other 2 had normal blood pressure. Punctate hemorrhages of the type associated with diabetes were found in twenty-three fundi of the 12 patients. After three months of treatment with rutin, improvement was found in the eye grounds of only 5 of these 12 patients. Of this group of 5 patients only 2 showed improvement in both retinal picture and fragility of the capillaries of the skin. Both of these patients had hypertension but the blood pressure returned to normal while they were under observation. It might be pointed out that although increased capillary fragility may play a role in producing retinal hemorrhages, factors such as severe exertion or hypoglycemic reactions to insulin may precipitate retinal hemorrhages in diabetic patients. Moreover, some investigators (*Nutrition Reviews* **5,** *81* (*1947*)) have noted improvement in retinal hemorrhages in patients on a high protein diet. These authors conclude that it is difficult to ascribe any of the results obtained in the treatment of capillary fragility to rutin.

The second article (R. Rodriguez and H. F. Root, *New Engl. J. Med.* **238,** *391* (*1948*)) reports a study of 100 unselected diabetic patients and 56 additional patients selected because of the presence of definite retinopathy. Capillary fragility was measured by Göthlin's positive pressure method. Of the 100 unselected patients the capillary fragility was increased above normal in 40, borderline in 4, and normal in 56. There was a good correlation between abnormal capillary fragility and hypertension and diabetic retinitis—in only 3 patients with capillary fragility increase were both the blood pressure normal and retinitis absent. In the group of 56 selected patients with diabetic retinopathy the capillary fragility was increased in 84 per cent, borderline in 16 per cent, none being normal. Thus, in the series of 156 patients, there were 82 with retinitis, of whom 43 had hypertension. The duration of the diabetes seemed to correlate better with the incidence of retinitis than did age.

Rutin, 20 mg. daily, was administered to 70 patients of whom only 20 were adequately followed. In these 20, the dosage was increased to 120 to 180 mg. daily and continued for several months. The capillary fragility became normal or borderline in 5 cases (25 per cent), improved in 5 (25 per cent), but was unimproved in 10 (50 per cent). However, in no instance was retinitis improved. In fact, there was evidence of progression in 4 while on rutin therapy (these patients showed no improvement in capillary fragility). There were no signs of toxicity to the rutin administered, nor was there significant change in the blood pressure. The authors conclude that although the commonly found capillary fragility may be brought to normal in diabetic patients by the prolonged administration of rutin, no change in retinitis can be expected.

J. B. Wolffe and A. W. Danish (*J. Am. Med. Assn.* **134,** *692* (*1947*)) reported the occurrence of subconjunctival hemorrhage during the administration of rutin. Neither of their patients had diabetes but both had hypertension. The capillary fragility tests were normal in both these patients at the time of the appearance of the hemorrhages.

These data suggest that rutin may have a definite activity in decreasing capillary fragility as measured by the positive pressure method, but that it is not of much, if any, therapeutic benefit to diabetic patients.

Rutin is a substance belonging to the group of flavone glucosides, the first of which to be described as of medical interest was hesperidin (vitamin P). Extensive animal studies on deficiencies of these substances have led to conflicting results. That

they may have an important place in advancing our understanding of certain hemorrhagic conditions is indicated by the brief report of P. E. Rekers and J. B. Field (*Science* **107,** *16* (*1948*)). These investigators found that the hemorrhagic lesions induced in dogs by a single (mid-lethal) dose of x-irradiation were to a large measure prevented, and survival greatly prolonged by administration of rutin. This occurred despite a similar thrombocytopenia in both control and rutin treated animals, except that both thrombocytopenia and an observed leukopenia disappeared after ten to fourteen days in those given the glucoside. These studies indicate that under certain circumstances, at least, rutin has a definite antihemorrhagic tendency.

RELATION OF HIGH CHOLESTEROL DIET TO PLACENTAL TRANSFER OF VITAMIN A

C. J. Lund and M. S. Kimble (*Am. J. Obstet. Gynec.* **46,** *207* (*1943*)) suggested that transfer of vitamin A to the human fetus may be related to, or even limited by, the lipid metabolism of the placenta and that there was no correlation between maternal and fetal plasma vitamin A levels. These authors and others have observed that the concentration of vitamin A in the fetal liver and plasma has been consistently lower than that found in maternal liver and plasma. T. L. Terry (*Am. J. Ophth.* **25,** *1409* (*1942*)) and others observed that pregnant animals severely deficient in vitamin A, produced fetuses with malformations of the eye which are similar to the fibroplasia found behind the lens in some premature infants. The severity of the deficiency required to produce these changes was sufficiently extreme that most of the fetuses were resorbed and only rarely were live young born (J. Warkany and E. Schraffenberger, *Proc. Soc. Exp. Biol. Med.* **57,** *49* (*1944*)).

Since feeding a high cholesterol diet to rabbits has been observed to cause a large deposition of cholesterol esters and some excess neutral fat in the placenta (G. Popják, *J. Physiol.* **105,** *236* (*1946*)), M. B. Williamson (*J. Biol. Chem.* **174,** *631* (*1948*)) conducted a series of experiments using Popják's procedure to determine whether the deposition of lipids in the placenta of the rat would depress the permeability of the placenta to vitamin A. If this did occur, the fetuses would thus be deprived to a greater degree of vitamin A than the maternal organism. The investigator speculated that a higher susceptibility of the fetal rat to the fibroplasia syndrome might be produced without as high an incidence of fetal resorption.

In the first experiment, female rats were maintained on a vitamin A deficient diet from weaning until the growth curve plateaued about six weeks before the rats were to be bred. A total of 325 I.U. of vitamin A was given to each rat in a sixty-three day period. Prior to breeding, the rats were divided into two groups, one of which was maintained on the basal vitamin A deficient diet, while the other was fed the basal ration plus the addition of 2.5 per cent of reprecipitated cholesterol at the expense of sucrose. In the second experiment, the procedure was modified by administration of only 95 I.U. of vitamin A during a fifty day period and by an increase in the cholesterol content from 2.5 to 5.0 per cent. A third experiment was attempted in which 8.0 per cent of cholesterol was fed but which could not be completed due to resorption of the fetuses.

Shortly before completion of gestation, maternal blood samples were taken by heart puncture. The rats were then killed and the fetuses removed. The whole fetuses or fetal livers, maternal liver and blood

samples, and a number of placentas were analyzed for vitamin A content. Placental fat was determined from an ether extraction of an acidified, alkaline hydrolysate.

The plasma and liver vitamin A values for the maternal rats were not altered by administration of these amounts of cholesterol in the ration. The values for both groups of animals in the first experiment were considerably higher than for both groups on the second experiment because of the higher amount of vitamin A administered in the period before breeding. On this basis, the same amount of vitamin A would be expected to be available for placental transfer in the control as in the experimental animals of the individual experiment, but to be appreciably less for all animals in the second experiment than for those in the first. The values for placental vitamin A were not believed to be highly reliable because of the small amount of tissue available for analysis. No difference between the vitamin A content of the placentas from control and experimental rats was observed. The ether-extractable lipid fraction from the placentas showed widely divergent values for the animals fed cholesterol and for the controls with average values of 1.85 and 4.53, respectively, on the basis of fresh tissue. In the first experiment, the control fetal livers contained 50 per cent more vitamin A than was found in the livers of the fetuses from rats fed 2.5 per cent cholesterol. In the second experiment, the vitamin A content of the entire fetuses was significantly greater for those from control rats than for those fetuses from rats fed 5.0 per cent cholesterol. However, the level of vitamin A in the fetuses from control rats was much lower than that of fetuses from rats maintained on a normal stock ration. The latter difference was undoubtedly due to the restricted amount of vitamin A provided to these control female rats in the period before and during gestation.

These data demonstrate that there exists an inverse relation between the lipid content of the placenta and the transfer of vitamin A from the maternal to the fetal body. This relation appears to be independent of the state of vitamin A nutrition of the maternal organism. No data were presented to indicate the effect on fibroplasias of the fetal eye during these experiments. The fact that there was a resorption of the fetuses in the third experiment when 8.0 per cent cholesterol was fed to the pregnant rats would seem to indicate that an even more serious effect on the transfer of vitamin A had occurred in this group of rats. Possibly some level of cholesterol between 5.0 and 8.0 per cent might result in a state of vitamin A metabolism adequate for the mother and the maintenance of the placental-uterine relation, but inadequate for the development of a normal fetus.

PANTOTHENIC ACID IN THE NUTRITION OF THE HEN

The identity of the yeast growth factor, pantothenic acid, with a vitamin required by animals was first proved with chicks, and this species is still perhaps the most convenient experimental animal for work with this vitamin. While chicks require a dietary source of pantothenic acid for growth, mature hens remain in rather good condition for considerable periods of time on diets containing very little pantothenic acid, and continue to lay eggs. The hatchability of eggs laid by hens on such a ration, however, rapidly falls to zero.

In previous studies, the amount of pantothenic acid necessary to maintain high hatchability in eggs was found to lie between 1200 and 1700 micrograms per 100 g. of ration. This value was determined on a ration freed from pantothenic acid by heat treatment. Even when supplemented with

large amounts of pantothenic acid, such a ration does not permit production of eggs of optimal hatchability, and the possibility remained that the requirement for pantothenic acid thus determined was augmented by deficiencies of other factors in the heated ration.

M. B. Gillis, G. F. Heuser, and L. C. Norris (*J. Nutrition* **35,** *351 (1948)*) have reinvestigated this problem. For this purpose, the heated ration formerly used was replaced with one composed of natural foodstuffs known by microbiologic assay to be low in pantothenic acid, supplemented with vitamins and a salt mixture. The ration contained approximately 150 micrograms of pantothenic acid per 100 g. by microbiologic assay. In one experiment, six lots of 8 hens and one male each were maintained on the experimental ration supplemented with various amounts of pantothenic acid; in a second experiment, six lots of 10 hens and 2 males each were maintained on these rations for fifteen weeks. The males were rotated frequently among the different lots to eliminate differences in breeding capacity. Eggs were incubated weekly and fertility and embryonic mortality determined by candling at intervals.

In both experiments, the average weight of the hens increased during the experimental period and their general physical condition was good at the end of the trials. Egg production remained constant in one experiment, and actually increased during the other. Despite these evidences for adequacy of the ration, the hatchability of eggs produced fell steadily from an initial value of 93 to 95 per cent to 0 per cent at ten weeks. In the first experiment, 750 to 1000 micrograms of pantothenic acid were required to maintain high hatchability. In the second experiment, conducted with hens more rigorously selected for production of eggs of high hatchability, 650 micrograms per 100 g. of ration sufficed. These results show first, that the dietary requirement for pantothenic acid for production of eggs of high hatchability is considerably lower than previously supposed, presumably because a more complete ration was fed, and secondly that the maintenance requirement of the adult fowl for pantothenic acid is not greater than about 150 micrograms of pantothenic acid per 100 g. of diet. This is about 25 per cent of that of the growing chick and about 20 per cent of that required for production of eggs of high hatchability. It is possible, however, that the experimental period was not sufficiently prolonged to produce symptoms of deficiency in the hens, and that the actual requirement for maintenance is higher than that indicated by this study.

The rapidity with which the hatchability of eggs returns to normal following supplementation of the diet of the hens with pantothenic acid is striking. During the tenth week, for example, the hatchability of eggs from hens on the basal diet had fallen to zero. When the ration was supplemented at this time with 800 micrograms of pantothenic acid per 100 g., hatchability of eggs laid during the eleventh week was 40 per cent, and those during the twelfth week had normal hatchability (96 per cent).

Chicks which hatched from eggs from hens receiving only 350 micrograms of pantothenic acid per 100 g. of ration (hatchability of eggs, 76 per cent) were somewhat lighter than those from hens more liberally supplemented, and the mortality rate of such chicks was also high. There is thus no doubt that this level of pantothenate was insufficient in the ration of the breeder hens. No characteristic abnormality in unhatched embryos from deficient eggs could be detected. This differs from the situation found in riboflavin deficient or in biotin deficient embryos (J. R. Couch, W. W. Cravens, C. A. Elvehjem, and J. G. Halpin, *Anat. Record* **100,** *29 (1948)*) where characteristic deformities in the embryo are found.

Analyses for pantothenic acid in the blood and in the eggs of hens receiving various dietary levels of pantothenate were con-

ducted. Blood levels were linearly related to concentration of pantothenate in the diet within the range from 4 to 11 micrograms of pantothenate per gram of diet. Above or below these values, however, the curve flattened out, a fact which suggests that the animal attempts to maintain the pantothenate content of the blood between certain limits, presumably by controlling the rate of its excretion. Analyses of eggs confirmed previous results (E. E. Snell, E. Aline, J. R. Couch, and P. B. Pearson, *J. Nutrition* **21,** *201 (1941)*; Pearson, V. H. Melass, and R. M. Sherwood, *Arch. Biochem.* **7,** *353 (1945)*) which showed that the pantothenic acid content of the eggs is linearly related to that of the diet over a wide range of concentrations.

The results of this study emphasize again the gap which may and often does exist between dietary requirements for growth, for maintenance, and for special functions such as reproduction. The latter phase of nutritional science still remains largely unexplored.

UTILIZATION OF D-TYROSINE FOR RAT GROWTH

Tyrosine which is usually classified as a nonessential amino acid has been shown by W. C. Rose and M. Womack (*Nutrition Reviews* **5,** *180 (1947)*) to be capable of replacing in the growing rat about one half of the requirement for the essential amino acid, phenylalanine. The observations of these investigators were based on an assay where a growth stimulus resulted when tyrosine was added to a diet containing an inadequate amount of phenylalanine. The presence of 0.8 per cent of tyrosine allowed good growth in the presence of 0.4 per cent of phenylalanine instead of 0.9 per cent which is the normal requirement for growth in the absence of tyrosine.

Using the same type of assay, E. C. Bubl and J. S. Butts (*J. Biol. Chem.* **174,** *637 (1948)*) tested the availability to the growing rat of the unnatural D-tyrosine as compared with the natural form, L-tyrosine. At 28 days of age, 3 litters of rats of the Long-Evans strain were distributed into groups with respect to weight, litter, and sex and placed in individual cages. The amino acid mixture used to supply the known essential amino acids was prepared from crystalline amino acids of excellent analytical purity. Phenylalanine was supplied at a level of 0.5 per cent. The growth of rats was compared when L-tyrosine, D-tyrosine, and DL-tyrosine, each at a level of 0.5 per cent, were added. Also, the effect of the addition of 0.25 per cent of L-tyrosine was tested. No difference in growth response was observed when D-, L-, or DL-tyrosine were fed at the 0.5 per cent level. Removal of tyrosine from the diets at the end of a twenty-eight day experimental period resulted in an immediate weight loss for all groups. The rate of growth of the rats receiving the 0.25 per cent supplement of L-tyrosine was appreciably less than for those receiving a 0.5 per cent supplement of D-, L-, or DL-tyrosine. These data demonstrate that in the presence of a suboptimal amount of phenylalanine, the D- isomer of tyrosine was completely available to the growing rat either in the DL-racemic mixture or alone. This conclusion is in keeping with the *in vitro* studies of N. L. Edson (*Biochem. J.* **29,** *2498 (1935)*) which indicated that both isomers were degraded to the same extent and in the same manner by various animal tissues. In this regard tyrosine is comparable to tryptophan, phenylalanine, methionine, and histidine in that both enantiomorphs of the amino acid can be used for growth by the rat, and unlike valine, leucine, isoleucine, threonine, and lysine where only the natural isomer is utilizable.

Available data on the utilization of D-tyrosine by human subjects are limited to that of A. A. Albanese, V. Irby, and M. Lein (*J. Biol. Chem.* **166,** *513 (1946)*) who concluded from excretion studies after administration of 0.01 mole of DL-tyrosine that sufficient tyrosine and aliphatic organic acids were excreted to account for nearly all of the D-tyrosine in the racemic mixture. From this indirect evidence, which does not demonstrate conclusively that those excretory products came exclusively from D-tyrosine, they postulated that the D- isomer was poorly or totally utilized by man. Again, the fact that these human subjects were adults and not in a period of active growth may aid in explaining this discrepancy in data. If this difference in availability between man and the rat can be demonstrated, an interesting and unusual species difference will have been established.

PTEROYLGLUTAMIC ACID (FOLIC ACID) DEFICIENCY IN SWINE

The discovery of the effectiveness of pteroylglutamic acid in producing an hematopoietic response in pernicious anemia and related disorders has failed to clarify the pathogenesis of these anemias. Neither pteroylglutamic acid nor its naturally occurring conjugate, the heptaglutamate, appears to be the extrinsic factor, the intrinsic factor, nor the potent antipernicious anemia substance in purified liver extract. Because the role of pteroylglutamic acid in metabolism is still so obscure, experimental studies are of special interest.

G. E. Cartwright, J. Fay, B. Tatting, and M. M. Wintrobe (*J. Lab. Clin. Med.* **33,** *397 (1948)*) describe the hematologic manifestations of pteroylglutamic acid deficiency in swine produced by administration of a synthetic substance having an action antagonistic to that of pteroylglutamic acid. The antagonist used ("crude methyl folic acid") antagonizes reversibly the effect of pteroylglutamic acid on the growth of Streptococcus faecalis R and of Lactobacillus casei.

For the study, 12 weanling Chester White pigs, 21 to 28 days of age, were used. Eight animals served as controls and 4 were given the antagonist as well as sulfasuxidine, the latter forming 2 per cent of the basal diet. This last consisted of crude casein, 10 per cent, as well as sucrose, lard, a complete salt mixture, vitamins A and D, and all of the "B vitamins" available in crystalline form except pteroylglutamic acid, para-aminobenzoic acid, and inositol. The antagonist was administered daily in capsules in amounts of 0.2 per cent of the basal diet, an amount equivalent to 0.06 g. per kilogram of body weight. The animals receiving the antagonist were first depleted of pteroylglutamic acid for periods of eighty-six to one hundred and twenty-two days by feeding the diet lacking pteroylglutamic acid and supplemented with sulfasuxidine.

To determine whether extrinsic factor is present in the crude casein fed these animals, the material was assayed by the accepted procedure in 3 patients with classic uncomplicated Addisonian pernicious anemia. It was demonstrated that extrinsic factor was present in the casein in an amount sufficient to produce a reticulocyte response in the patients.

The animals receiving the antagonist became listless and weak and ate poorly. Hair loss was not extensive but the hair became thin and lusterless. The general appearance of the animals was extremely untidy, the abdominal walls sagged, and moderately severe diarrhea was present. Impairment of growth was not great as compared with that of the control animals receiving the low casein diet not deficient in pteroylglutamic acid.

In contrast to the control animals, those

receiving the antagonist became markedly anemic in twenty-one to forty-two days. The volume of packed red cells decreased from a level of about 35 ml. to approximately 20 ml. per 100 ml. The anemia at this time was normocytic. Unusually large macrocytes were seen but microcytes were equally numerous. A mild leukopenia and severe neutropenia also developed. The percentage of granulocytes was reduced to 14 as compared with the mean of 47 per cent for the control group. The number of platelets per cubic millimeter of blood in the control animals was somewhat higher than in those receiving the antagonist.

The bone marrow from the animals receiving antagonist revealed a marked reduction in the number of polymorphonuclear neutrophils and neutrophilic metamyelocytes as well as a slight increase in earlier forms of the myeloid series and a significant decrease in the leucocyte-erythroid ratio. In addition, extremely immature and somewhat abnormal nucleated red cells were present. The authors state that these cells resembled closely the megaloblastic cells seen in the marrow of patients with pernicious anemia. They were unlike cells seen by them in the marrow of the control animals and in marrows of pigs following severe and prolonged hemorrhage superimposed on the dietary restriction of iron.

There was no significant difference in either the plasma iron or in the free erythrocyte protoporphyrin values in the control group and in those receiving antagonist. Animals maintained on the low protein diet were found to have a significantly reduced serum copper.

The influence of therapy is of special interest. An increase in the quantity of casein fed to one of the animals was associated with a temporary increase in volume of packed red cells, but this was not sustained and the animal became severely anemic. There was no change in leucocytes or reticulocytes.

Three animals were treated with purified liver extract; in one there was no significant effect on any of the blood constituents; in the other 2 there was a suboptimal response consisting of a reticulocytosis of 15 per cent in one animal and a modest rise in volume of packed red cells and platelets in both. In one pig the total leucocyte count had risen to normal at the time liver therapy was begun. There was no apparent effect from the liver therapy and neutropenia developed again. In the other animal the total leucocyte and neutrophil values rose to normal but were not sustained. When these 3 animals were treated with synthetic pteroylglutamic acid an immediate rapid and maximal increase in the volume of packed red cells followed. In 2 of the pigs a significant reticulocytosis appeared. An initial rise in the platelet count was observed in 2 of the animals, but in 3 in which the platelets were followed for a significant period of time, thrombocytopenia reappeared. In 2 of the pigs the leukopenia and neutropenia disappeared following pteroylglutamic acid therapy.

All 3 of the pigs treated initially with liver developed definite but not marked macrocytosis following liver therapy. After treatment with pteroylglutamic acid the macrocytosis disappeared and the anisocytosis and polychromatophilia likewise disappeared. One pig was treated initially with pteroylglutamic acid and this was followed by an immediate reticulocytosis. At the same time there was a rapid rise in the volume of packed red cells and an increase in the neutrophil count. As to the bone marrow, administration of liver extract was associated with a diminution in the number of megaloblasts in each instance but did not result in complete disappearance of these cells, which occurred only following administration of pteroylglutamic acid.

These observations indicate that there is a marked difference between the effect of pteroylglutamic acid and that of liver extract of the pernicious anemia type in pigs

fed low protein diets receiving a folic acid antagonist. These results are not in accord with those of R. W. Heinle and co-workers (*Proc. Central Soc. Clin. Res.* **20,** *7 (1947)*) who concluded that "Extrinsic factor and purified liver extracts are effective even though folic acid is not available to the animal." This difference in results may be related to differences in the experimental conditions employed by the Cleveland workers and those in Utah. Of possibly greatest significance is the fact that the animals used by the Cleveland group were given a vitamin-free casein containing little or no extrinsic factor.

As the writers themselves point out, their observations leave many questions unanswered and one still waits for a clarification of the relation of pteroylglutamic acid and liver extract. It is encouraging, however, that at last a cellular response has been produced in the bone marrow which is closely similar, if not identical, to that observed in human pernicious anemia.

BIOCHEMICAL FUNCTION OF INSULIN

The biochemical picture in diabetes or in the depancreatized animal leads to the conclusion that either carbohydrate oxidation is markedly inhibited or that fat is converted to glucose. With satisfactory evidence for the latter lacking, the former viewpoint is most generally accepted. It is difficult, however, to support the thesis that insulin is indispensable for carbohydrate oxidation. Thus it is well known that the brain is dependent on carbohydrate oxidation, yet central nervous system function is not markedly affected in the depancreatized animal. Normal blood levels of certain carbohydrate intermediates such as lactate and pyruvate are found in diabetes or in the depancreatized animal. Finally, the case of the "Houssay dog" is pertinent, where despite the absence of the pancreas (and the hypophysis), carbohydrate oxidation appears essentially normal.

In attempting to localize the action of insulin by physiologic experiments (as contrasted with isolated tissue studies), several reports indicate that the action is concerned with the early phases of glucose oxidation. Thus the normal blood pyruvate response obtained on administration of glucose is absent in the depancreatized dog or diabetic patient unless insulin is given simultaneously (E. Bueding, J. F. Fazekas, H. Herrlich, and H. E. Himwich, *J. Biol. Chem.* **148,** *97 (1943)*; Bueding, H. Wortis, and H. D. Fein, *Am. J. Med. Sci.* **204,** *838 (1942)*). In harmony with these findings is the mechanism of insulin action suggested by the experiments of W. H. Price, C. F. Cori, and S. P. Colowick (*Nutrition Reviews* **4,** *78 (1946)*) in which the enzyme hexokinase (glucose → glucose-6-phosphate) is implicated. The experiments of C. A. Villee, F. M. Sinex, and A. K. Solomon (*Federation Proceedings* **7,** *197 (1948)*) have been offered in support of the action of insulin on hexokinase. These investigators studied rat diaphragm muscle in mediums containing radioactive glucose. The addition of insulin to the medium increased both glucose oxidation and storage as glycogen, these processes being followed by tracing the C^{14}. Glucose oxidation was lower in muscle from alloxan-diabetic rats. Nevertheless, the original hexokinase experiments are in some dispute (*Nutrition Reviews* **6,** *8 (1948)*), and were never claimed to represent the sole possible action of insulin.

Certainly one of the most striking physiologic disturbances in diabetes is the failure to store liver glycogen, and administration of insulin causes a prompt restoration of liver glycogen. R. H. Broh-Kahn and I. A. Mirsky (*Arch. Biochem.* **17,** *367 (1948)*) have adopted the stand that the pre-

dominant insulin effect should be found in the reactions involved in the glucose ⇄ glycogen equilibrium. They were unable, however, to find any appreciable effect of insulin on the phosphorylase, phosphoglucomutase, or glucose-6-phosphatase systems in liver extracts—enzyme systems involved in the above reaction. They had previously been unable to confirm the experiments on insulin and hexokinase (*Nutrition Reviews* **6,** *8 (1948)*). They appear to resort for the moment to theories of insulin action which involve the intact cell rather than specific enzyme systems. Although there is some support for such a view, it is unfortunate that this view is not readily susceptible to rigorous experimental testing.

It must be pointed out that the initial phases of carbohydrate metabolism may be affected *in vivo* by insulin without involving the enzymes immediately concerned. Thus it is known that the initial phosphorylation of glucose is dependent on adenosinetriphosphate (ATP), and that the latter is synthesized by reactions which may be far beyond the initial stages of carbohydrate metabolism. Pertinent in this respect may be the experiments of N. Kaplan and D. M. Greenberg (*J. Biol. Chem.* **150,** *479 (1943)*) who found an increase of P^{32} in the ATP fraction of liver after the administration of insulin and radioactive phosphate to rats. E. S. Goranson, J. E. Hamilton, and R. E. Haist (*Ibid.* **174,** *1 (1948)*) have confirmed the earlier finding of J. Sacks (*Science* **98,** *388 (1943)*) that insulin caused an increased incorporation of P^{32} in the ATP of resting muscle. Because of the basic importance of ATP in energy transfers, a role of insulin in ATP formation or oxidative phosphorylation could account for apparent multiple functions of insulin.

Several other studies indicate that insulin affects later phases of carbohydrate metabolism, for example, the oxidation of pyruvic acid. Earlier studies on insulin effects concerned with the "citric acid cycle" suffered from technical difficulties, but the studies of L. Rice and E. A. Evans (*Science* **97,** *470 (1943)*) seemed to show that insulin sustained the respiration of pigeon breast muscle by maintaining pyruvate oxidation. This has been confirmed by a study of W. C. Stadie, N. Haugaard, and M. Perlmutter (*J. Biol. Chem.* **172,** *567 (1948)*) who have concluded from their experiments with minced pigeon muscle that insulin is involved in pyruvate oxidation, possibly in its condensation with four carbon dicarboxylic acids. It was obviously difficult to control the experimental conditions since one third of the experiments did not show the insulin effect. Even the general nature of the phenomenon might and has been questioned since entirely negative effects have been found with rat muscle.

One of the most interesting developments in this subject is the probable role of insulin in the biologic conversion of carbohydrate to fat. With the newer view that this transformation is a normal pathway of carbohydrate metabolism, rather than merely a mechanism called into play when carbohydrate intake is excessive, such a role of insulin takes on added significance. It may be recalled that D. R. Drury (*Am. J. Physiol.* **131,** *536 (1940)*) suggested that insulin is directly concerned in the conversion of carbohydrate to fat. In his experiments with depancreatized rats administration of insulin and carbohydrate led to a greater retention of sugar than could be accounted for by glycogen storage and oxidation, in contrast to control periods when insulin was not given. The failure of fat formation from carbohydrate in alloxan diabetes has been conclusively demonstrated by the isotope experiments of DeW. Stetten and G. E. Boxer (*Nutrition Reviews* **3,** *213 (1945)*). In these experiments the synthesis of fat was decreased to only 5 per cent of normal as judged by the incorporation of deuterium from the body fluids. These results do not prove a direct effect of insulin on the enzyme systems involved in the synthesis of fatty acids. Since the latter process requires energy,

probably through the intermediation of ATP, this transformation could be dependent on carbohydrate oxidation which provides for ATP synthesis. As suggested previously, the common basis for insulin action might therefore be in the synthesis of ATP.

Recent experiments with rat liver slices emphasize the importance of the role of insulin in fatty acid synthesis. Prior to isotopic tracing, studies of fatty acid synthesis *in vitro* were greatly retarded by the difficulties of analysis. The newer technic opens this field to new advances. Thus K. Bloch and W. Kramer (*Federation Proceedings* **7,** *146* (*1948*)) have shown that the incorporation of carboxyl-labeled acetate into fatty acids by liver slices is increased four to eightfold by the presence of pyruvate in the medium. Further studies of K. Bloch and W. Kramer (*J. Biol. Chem.* **173,** *811* (*1948*)) have revealed a pronounced action of insulin on the incorporation of isotopic acetate into fatty acids. In a system composed of a physiologic bicarbonate medium, carboxyl-labeled acetate, and rat liver slices, incorporation of isotopic carbon in the fatty acids was studied. The incorporation was significant when pyruvate, glucose, or glucose plus insulin were present in the medium, but when the combination of pyruvate plus insulin was present in the medium, the incorporation was two to threefold as great. These preliminary experiments suggest that at least one of the actions of insulin is concerned specifically with utilization of pyruvate for synthesis of fatty acids.

Certainly the precise mechanism of insulin action is not yet well defined, but its role in carbohydrate to fat transformation offers a unified picture for the biochemical defect in diabetes. It will be recalled that either "underutilization" or "overproduction" of glucose must be called upon to explain the excessive amounts of glucose excreted and present in the diabetic organism. The latter hypothesis, to the exclusion of the former, unfortunately leads to postulating the formation of glucose from fat. As an alternative, Stetten and Boxer (*loc. cit.*) calculated that the decreased formation of fat in the diabetic animal could account for the glucose excreted by the diabetic animal. On the balance sheet which does not account for fat formation, conversion of fat to carbohydrate is equivalent to a decreased fat synthesis from carbohydrate. Thus if a normal metabolic pathway of glucose metabolism is conversion to fat, possibly the nature of "underutilization" of glucose in diabetes is the failure of this conversion.

THE METABOLIC RATE IN SEMISTARVATION

As a result of their classic study of the effects of prolonged restricted diet, F. G. Benedict, W. R. Miles, P. Roth, and H. M. Smith ("Human Vitality and Efficiency under Prolonged Restricted Diet," *Publication* **280,** *Carnegie Institution of Washington* (*1919*)) concluded that the observed depression in the total metabolism was the most prominent feature of their entire research, and that this decreased metabolic rate was accompanied by a similar depression in other physiologic functions such as blood pressure and pulse rate. These workers emphasized that the observed decrease in metabolic rate was greater than the decrease in body weight or surface area. They hypothesized that the depression of metabolism was due to loss of body nitrogen (protein) during the course of underfeeding.

The decrease in metabolism which results from underfeeding has been confirmed by a more extensive modern investigation of experimental starvation (A. Keys, *J. Am. Dietet. Assn.* **22,** *582* (*1946*)). Keys reported a fall in metabolism per unit of body surface of approximately 30 per cent as a conse-

quence of six months of semistarvation. During the twenty-four week period of semistarvation, the basal oxygen consumption decreased from a mean of 229.2 ml. per minute to 140.6 ml. per minute, but the loss in body weight represented only 24 per cent of the control body weight. Measurements of body water revealed that at the end of semistarvation there was an average excess of about 12 to 16 pounds of water in the body so that the actual tissue loss was considerably greater than the weight loss. When allowance was made for the water retention and the basal metabolism per unit weight of active tissue was calculated, the decline in metabolism was approximately 10 per cent, a figure less than that which has been widely accepted as occurring as a result of semistarvation. Thus it appears that the downward adjustment of metabolism in starvation is due largely to the loss of actively metabolizing tissue and not primarily to a reduction in the metabolic rate of specific tissue mass.

Both of these experimental investigations were made on otherwise healthy individuals maintained on a diet which was prepared in the laboratory and which was not too poor of quality except for the quantity of calories supplied. Observations on undernourished individuals in famine areas are not only of confirmatory value but indicate whether the findings obtained from these experimental studies on starvation are strictly applicable to conditions encountered in practical field experience. Mention has already been made of such comparisons treating the mechanism of famine edema (*Nutrition Reviews* **6,** *110 (1948)*).

Observations on the metabolic rate of severely undernourished German adults have been reported by J. Beattie and P. H. Herbert (*Brit. J. Nutrition* **1,** *185 (1947)*). These workers were impressed with the great discrepancies existing between the observed levels of basal metabolism when expressed in terms of heat production per square meter of body surface on the one hand, and when calculated as heat production per kilogram of body weight on the other. These discrepancies in undernourished persons became greater with increased weight loss. To study the point, they selected a group of 11 undernourished men, otherwise free of organic disease and whose basal oxygen consumptions did not vary more than 5 per cent from day to day over a two week preliminary period. All of these men had been detained in a civil prison from July, 1945, to July, 1946, and the fall in body weight during the period could be obtained from the monthly weighings which had been carried out. The assumption was made that in their normal (well nourished) state, the heat production per square meter of body surface of these subjects approximated the standard tables devised by W. M. Boothby and I. Sandiford (*Am. J. Physiol.* **90,** *290 (1929)*) less a deduction of 5 per cent for training (*Nutrition Reviews* **4,** *34 (1946)*). The surface area of the body during semistarvation was calculated from the observed weight and height. The recorded weight losses of these subjects approximated 25 per cent over the period of one year. This loss was practically identical with the 24 per cent decrease in weight produced by semistarvation in the subjects of the Minnesota experiment (Keys, *loc. cit.*).

In Beattie and Herbert's series, the average decrease in heat production, when expressed as calories per square meter per hour, was 16 per cent. Simultaneously, the decrease in body weight per unit of surface area was 14.2 per cent. These findings were taken to indicate that the fall in heat production per square meter was a mere reflection of the fall in body weight per square meter. Furthermore, these workers found no significant difference in heat production per kilogram of body weight. Beattie and Herbert state that the total volume of the extracellular fluid (thiocyanate space volume) in the body showed no significant change in absolute amount in starvation from that in the normal state. On the other hand, the body fat was greatly diminished. Since body fat, due to its slow utilization of oxygen, may be

regarded as inert matter during short periods of oxygen consumption measurements, the suggestion seems reasonable that as the body weight falls the absolute loss of body fat may be compensated for by retention of extracellular water. Hence, the ratio of active to inert material in the body may show no significant change. With these considerations an estimate of body substance which was active metabolically was made and the heat production per kilogram of active material calculated. The heat production during starvation, when expressed as calories per kilogram of active material, appears to be identical with that during health. Theoretically, this method of expression should be preferable, but the data at hand did not permit the authors to conclude that active substance was a more useful index of basal metabolism than body weight. A probable explanation of this failure is that the percentage of active material in the body shows practically no change until the weight loss has exceeded 26 per cent.

This study of "naturally occurring" starvation and the investigation of Keys (*loc. cit.*) of experimental starvation indicate that during caloric undernutrition the oxidative rate of the active tissues deviate little, if at all, from the metabolic rate of the active mass under normal conditions. The observed decrease in basal metabolism is almost completely accounted for by the decrease in mass of active tissue.

ANTIMETABOLITES AS ESSENTIAL NUTRIENTS

The Woods-Fildes hypothesis of metabolite-antimetabolite interaction has become so well established as a result of repeated confirmations of its predictions that workers in this field are extending the list of microbial growth inhibitors to many new classes of compounds, each in its turn related structurally to a certain metabolite. Although these analogues are usually much less effective than the metabolites on a molar basis, the vast majority fit into the pattern of inhibiting synthesis, utilization, etc. of the metabolites (a few are inert or stimulatory) and the action of certain antibiotics is even sometimes viewed as being due to competition with metabolites, perhaps unknown, for specific enzyme functions.

In view of this extensive background of experience it seems highly improbable that an organism might exist in nature which would utilize an antimetabolite for growth, and that inhibition would be observed in the presence of the corresponding metabolite. Nevertheless this has been reported for at least one group of organisms.

S. Emerson and J. E. Cushing (*Federation Proceedings* **5,** *379* (*1946*)) in studies with mutant strains of Neurospora, obtained several which became "drug-fast" toward sulfanilamide. When one of the cultures which was tolerant to sulfanilamide was crossed with the wild type, a strain was segregated (E-13190) which exhibited little or no growth in the absence of sulfonamides, or in the presence of para-aminobenzoic acid at 10^{-5} to 10^{-2} mols per liter. Optimal growth was obtained in mediums containing 0.02 molar of sulfanilamide or sulfapyridine, or approximately 0.001 molar of sulfathiazole. Para-aminobenzoic acid in turn poisoned the mold (S. Emerson, *J. Bact.* **54,** *195* (*1947*)) and its action was antagonized by sulfanilamide. It thus seemed that the usual roles of the two compounds were reversed. In another experiment, a strain requiring sulfanilamide was crossed with a strain requiring para-aminobenzoic acid producing a new strain (E-16608A) which required both compounds simultaneously, with a ratio of sulfanilamide to para-aminobenzoic acid of about 100:1 being most satisfactory.

In further studies of the nutrition of these unusual mutants, M. Zalokar (*Proc. Nat. Acad. Sci.* **34,** *32* (*1948*)) investigated the growth-promoting properties of the folic acid group. A strain requiring para-aminoben-

zoic acid was first tested and it was found that pteroylglutamic acid and para-aminobenzoylglutamic acid were 1 to 2 per cent as active as para-aminobenzoic acid, and that pteroic acid was 5 to 10 per cent as active. The double mutant (requiring both para-aminobenzoic acid and sulfanilamide) grew in the absence of sulfanilamide with the first two of the folic acids, but when pteroic acid was supplied sulfanilamide was again required. The author pointed out that this behavior paralleled the known para-aminobenzoic acid content of these folic acid derivatives since they contained as impurities approximately 0.5 to 1.0 per cent, 0.1 per cent, and 6 per cent of para-aminobenzoic acid, respectively. It was felt that where the relative activity was higher than could be accounted for by the free para-aminobenzoic acid, the increase could be ascribed to slight cleavage during autoclaving or growth of the mold. To check this hypothesis, growth of the double mutant was carefully checked at low levels of para-aminobenzoic acid. In the concentration range 2×10^{-8} to 5×10^{-8} molar para-aminobenzoic acid, the double mutant responded rapidly to increasing levels, and to almost exactly the same extent as the wild type para-aminobenzoic acid-requiring strain. At higher concentrations of para-aminobenzoic acid growth of the double mutant diminished rapidly and could be restored with sulfanilamide.

From these observations, it is no longer necessary to view sulfanilamide as a metabolite for these mutants. Rather, as the author points out, it would appear simply that the tolerance of the double mutant to excess para-aminobenzoic acid is low, and that growth is inhibited by larger amounts of the vitamin. The "sulfanilamide-requiring" mutant apparently produces more than the tolerated amount of para-aminobenzoic acid and thus inhibits itself; sulfanilamide then acts as a detoxicant by virtue of its usual antagonistic action toward the vitamin.

In view of these studies, it seems possible that the observation that streptomycin is an essential nutrilite for certain organisms may also be an artifact. C. P. Miller and M. Bohnhoff (*Science* **105,** *620 (1947)*) reported that a variant (mutant) strain of meningococcus was produced which required streptomycin for growth either *in vitro* or *in vivo* in the mouse. The strain did not emerge until the concentration reached 40 micrograms per milliliter, but once established, 5 micrograms per milliliter were sufficient. These observations have been confirmed by G. Rake (*Proc. Soc. Exp. Biol. Med.* **67,** *249 (1948)*) who extended these studies to include mutant strains of Escherichia coli. Several of these showed wide tolerance to streptomycin, and one strain (D56) was stimulated by streptomycin in the range 20 to 80 units per milliliter.

Work by I. Rhymer, G. I. Wallace, L. W. Byers, and H. E. Carter (*J. Biol. Chem.* **169,** *457 (1947)*) indicates that lipositol is an active antagonist of streptomycin activity. The inositol-galactose structure of lipositol suggests a metabolite-antimetabolite relation. Lipositol was also found active by Rake for the growth of the "streptomycin-requiring" strains of E. coli, and it would seem possible that the situation here may parallel that of the double mutant in Neurospora. The response to lipositol is exhibited only within a limited range (20 to 160 micrograms of an impure preparation) above which streptomycin may be effective as an antagonist of the specific metabolite added or produced by the organism.

The work of Zalokar is helpful in that it dispels the phenomenal appearance of the earlier results with Neurospora, although much more work is needed to establish the exact metabolic role of streptomycin. The other papers discussed herein are significant nonetheless, for the strains of organisms studied may be considered as an extreme in "drug-fastness," and a moment's reflection will convince the reader of the importance of obtaining further knowledge of their nutrition.

MINERAL REQUIREMENTS OF FARM ANIMALS

Research during the past decade on mineral nutrition has brought about an extension of our knowledge of the quantitative requirements by various species. Although much of this knowledge has been gained incidentally to studies of mineral function, the importance of this information to the maintenance and improvement of the animal industries has also been recognized, and as a result separate studies have been made of the mineral requirements of farm animals. The data obtained range in abundance from virtually zero in the case of iron to the numerous reports which have been issued concerning calcium and phosphorus. Several of the important findings are discussed in an article by H. H. Mitchell (*J. Animal Sci.* **6,** *365 (1947)*), and the quantitative requirements have been tabulated for several species.

The importance of calcium, and more especially phosphorus, is of the first order in the nutrition of farm animals. Of the two elements, phosphorus, as the author points out, is not maintained in available body reservoirs; no mechanism corresponding to the parathyroid gland for the mobilization of calcium exists for phosphorus, and though large quantities are present in the skeleton, deficiencies are quickly manifested when dietary levels are low. The symptoms of depraved appetite, emaciation, and poor utilization of feed are accompanied by changes in the protein.

J. L. Hall, D. L. Mackintosh, and G. E. Vail (*Kansas Agr. Exp. Sta. Tech. Bull.* **58,** *22, 79 (1944)*) working with yearling steers observed that a low phosphorus diet produced beef of low palatability and keeping quality. Calcium deficiency, on the other hand, was found not to affect protein quality although bone strength was somewhat impaired. The fact that the protein was affected in this manner by phosphorus may lend weight to the suggestion by D. Rittenberg and D. Shemin (*Ann. Rev. Biochem.* **15,** *247 (1946)*) that the condensation of amino acids to form body proteins is preceded by phosphorylation.

Data obtained with Holstein heifers from birth to their first calving, and from Percheron colts revealed that the requirements of dietary calcium and phosphorus, expressed as percentages of dry feed, decreased sharply for the young calf during the first year, and more slowly thereafter. The calcium requirement dropped from 0.85 per cent of the dry matter to 0.18 per cent, and the phosphorus from 0.52 to 0.13 per cent during growth from 150 to 1200 pounds. The calcium:phosphorus ratio thus decreased also from 1.63 to 1.38. The results with colts were comparable, although extension of the age limit to 4 years revealed that the calcium requirement decreased to 0.06 per cent compared with a low of 0.09 per cent for phosphorus; the calcium:phosphorus ratio had thus dropped to less than 0.7.

The statement is generally made that the calcium and phosphorus requirements of the lactating female are high, and therefore similar to those of young animals. Actually the trends during gestation were almost exactly opposite from those observed during growth of the parent animal, due to the increasingly rapid development of the fetus toward the end of the gestation period. Thus, for sows, the calcium and phosphorus requirements during growth declined from 0.63 and 0.35 per cent at 3 months of age to 0.05 and 0.10 per cent at 19 months of age (calcium:phosphorus ratio dropped from 1.8 to 0.5) whereas the values rose during gestation to 0.43 and 0.29 (calcium:phosphorus ratio rose from 0.5 to 1.5).

Similar trends to those mentioned above have been observed among sheep and poultry (W. M. Beeson, R. F. Johnson, D. W. Bolin, and C. W. Hickman, *J. Animal Sci.* **3,** *63 (1944)*; Mitchell, *loc. cit.*). However, the sheep were found to require relatively less of these minerals, in a more nearly constant

amount during growth (calcium:phosphorus ratio dropped from 1.5 to 1.0 during the age range of 1 to 16 months). White Leghorn chickens, on the other hand, maintained very high requirements of both minerals. Increases in body weight from 0.5 to 4 pounds were accompanied by a decline in the calcium and phosphorus requirements from 0.71 and 0.36 per cent to 0.42 and 0.28 per cent, the calcium:phosphorus ratio dropping from 1.97 to 1.50.

The laying hen and the lactating animal represent special cases, for both lose large quantities of calcium and phosphorus daily. For cows and ewes the calcium requirements during lactation did not greatly exceed those during growth, but the phosphorus requirements were 30 to 50 per cent higher (Beeson, Johnson, Bolin, and Hickman, *Idaho Agr. Exp. Sta. Bull.* **266** (*1945*); Mitchell, *loc. cit.*). In the laying hen the more excessive requirement was for calcium, which was sometimes needed in excess of 3 per cent of the ration, depending upon the rate of egg production, whereas the phosphorus requirements approximated those during growth (R. J. Evans, J. S. Carver, and A. W. Brant, *Poultry Sci.* **23**, *9, 36* (*1944*)).

The need for sodium, potassium, and magnesium is doubtless universal throughout the animal kingdom; probably copper, iron, and iodine are similarly important. The need for manganese has been demonstrated only for poultry and for the rat, although it may also be required by the pig (S. R. Johnson, *J. Animal Sci.* **3**, *136* (*1944*)). However, the participation of manganese in arginase, and of zinc in carbonic anhydrase suggests their universality of appearance. Cobalt appears to be required only by ruminants. S. N. Ray and co-workers (*Ibid.* **7**, *3* (*1948*)) have supposed that one of its effects may be to aid in the synthesis of various "B vitamins" by the microflora of the rumen.

The maintenance of sufficient quantities of the trace elements in the diet of farm animals fortunately does not seem to be difficult in most areas, with the possible exceptions of cobalt and iodine. Iodized salt has proved satisfactory for the maintenance of iodine, and from the work cited above it would appear that an addendum of about 0.1 part per million of cobalt daily, based on the dry ration, would furnish protection against a deficiency of this element. However, too great fortification with cobalt, as well as with manganese or copper, may react unfavorably. Moreover, G. R. Sharpless and E. K. Anthony (*J. Nutrition* **25**, *239* (*1943*)) have reported that excess salt intake will bring about a reduction of the iodine content of the thyroid gland. It would appear that mineral supplements, when used, should be added in amounts calculated to fall within the recognized beneficial range.

The maintenance of calcium and phosphorus levels presents special problems, due to the need for maintaining an adequate supply of vitamin D as well as a proper balance between the two elements in the diet. Whereas grains are usually deficient in calcium, hays are often low in phosphorus. Proteins, however, are adequate in phosphorus, and those of animal origin which contain bone are rich in both elements. Moreover, there is a close correlation between protein and phosphorus requirement (H. H. Mitchell, *National Research Council, Committee on Animal Nutrition, Report No.* **10** (*1943*)) and it has been suggested that the inclusion of adequate levels of animal protein will insure sufficient phosphorus for animals under most conditions. When reliance has to be placed upon nonlegume hays for a major source of energy, supplementation with phosphate minerals is likely to be necessary.

NOTES

Alterations in the Absorption of Iron and Copper

D. M. Hegsted, T. D. Kinney, and J. A. Cartaya (*Am. J. Path.* **24,** *722 (1948)*) have reported briefly on experiments to study the ability of rats to absorb iron and copper when they were fed diets low in both protein and choline. When a supplement of 2.2 per cent of ferric citrate was added to the diet which contained only 8 per cent casein but which was adequate in minerals and vitamins other than choline, definite toxic manifestations occurred as judged by gross appearance, survival time, and weight losses of the rats. A supplement of 0.1 per cent copper sulfate alone was not toxic, but when given with the above supplement of ferric citrate resulted in more severe toxicity than the ferric citrate alone. Increases in the choline content of the diet did not alter the degree of toxicity but an increase in the casein content of the diet prevented all manifestations of toxicity. The iron content of the livers was found to be slightly increased in those animals with toxicity and some iron could be demonstrated in the liver on histologic examination. These observations were not believed to be sufficient to explain the toxicity signs observed. No alteration in phosphate absorption could be demonstrated since there was no significant difference in the percentage of bone ash in animals receiving the iron supplement and those receiving the control diet and since examination of the bone indicated no abnormalities.

These authors postulated a possible interrelation between copper and choline. The addition of adequate amounts of copper to a choline deficient diet largely prevented the deposition of excessive fat in the liver. In addition, when choline was added to the diet larger quantities of copper were present in the liver than in choline deficient rats.

These relations of protein metabolism to the absorption and utilization of iron and of choline and copper utilization are highly interesting ones which merit further systematic investigation especially in relation to human dietaries.

Growth Inhibitory Factor in Corn Bran

Indirect evidence for a growth inhibitory factor in corn bran has been reported in a preliminary communication by A. Borrow *et al.* (*Lancet* **I,** *752 (1948)*). Growth was markedly retarded in weanling mice during a six week period by the addition of corn bran at a 10 per cent level to a control diet, moderately low in protein (10 per cent). The control and bran diets contained, respectively, 103 and 104 mg. per cent of tryptophan and 0.12 and 0.37 mg. per cent of niacin. Inferior growth occurred during the first three weeks on the bran diet, and this was followed by loss of weight and some deaths. The mice became unkempt in appearance. The addition of 5 mg. per cent of nicotinamide to the bran diet at the end of the sixth week resulted in complete restoration of the normal healthy appearance but failed to cause gain in weight. Mice fed this supplemented diet from the beginning of the experiment grew as well as those on the control diets.

The retardation of growth in these experiments was not reversible by nicotinamide, indicating the possibility of permanent damage. Whether additional tryptophan would have been effective was not determined. It is worthy of emphasis that the deleterious effect of bran was not due to a lowering of dietary protein or of tryptophan. The data support the earlier finding of D. W. Woolley that corn contains an inhibitory factor (*Nutrition Reviews* **4,** *334 (1946)*; **6,** *77 (1948)*), but do not negate evidence of a niacin-tryptophan relation (*Ibid.* **3,** *267 (1945)*, **4,** *182 (1946)*, **5,** *110, 197 (1947)*). Because human pellagra continues to be a serious problem in many areas of the world, it is of importance to verify the existence of an

inhibitory factor in corn, to determine its nature, and to discover whether it is a significant factor in this nutritional deficiency disease which is so frequently associated with the use of corn as staple food.

Protein Putrefaction and Dental Caries Activity

S. Dreizen and T. D. Spies (*Nutrition Reviews* **6,** *207 (1948)*) observed that dilute solutions of either indole or indole-3-acetic acid, decomposition products of the amino acid tryptophan, inhibited the acid production of incubated saliva and the growth and acid production of a pure culture of Lactobacillus acidophilus (Hadley). These investigators have continued to study the inhibitory effect of various other products of protein putrefaction by the above procedures which have been recommended by various research groups as possible methods for studying dental caries activity (*J. Dental Research* **27,** *305 (1948)*).

Skatole was found to be significantly effective as an inhibitor of acid production in incubated saliva at amounts of 4.0 mg. or more per 10 ml. of saliva and to be able to inhibit completely the growth and acid production of L. acidophilus at the same concentration per 10 ml. of yeast extract dextrose broth. Phenol had similar inhibitory properties when added to 12.0 mg. per 10 ml. of saliva and was a mild inhibitor of growth and acid production at levels of 4.2 mg. or higher per 10 ml. of medium. Orthocresol had a definite inhibitory action on acid production in saliva at levels of 0.005 and 0.01 ml. per 10 ml. of saliva, and a strong inhibitory effect on growth and acid production of L. acidophilus at levels of 3.2 mg. or higher per 10 ml. of medium. Paracresol likewise was effective as an inhibitor at a concentration of 0.01 ml. per 10 ml. of saliva and a mild inhibitor of growth and acid production of L. acidophilus at levels in excess of 4.2 mg. per 10 ml. of nutrient broth. In saliva 1,4-diaminobutane dihydrochloride was a mild inhibitor at levels up to 10.0 mg. per 10 ml. of saliva but had no inhibitory effect on L. acidophilus at levels up to 15.0 mg. per 10 ml. of medium.

It is unknown whether these materials have any effect on the initiation and development of carious lesions in experimental animals or in man. Until such time as the compounds are tested in experimental animals, the above results can only be considered as indications of what might happen in the oral cavity if the premise is correct that acid production is the chief criterion for the initiation and development of carious lesions.

Flavor of Meat

The flavor of meat cooked at low temperature is developed almost entirely from the fibrous solid matter of the meat, rather than from the juice, according to a report by E. C. Crocker (*Food Research* **13,** *179 (1948)*). The work reported is of an organoleptic investigation of meat flavor. Beef was the principal meat studied, but some work was also done on pork, lamb, and chicken. Only relatively low temperatures, up to the boiling point of water, were used for developing the flavor.

Defatted beef was pounded, hydraulically pressed, and then leached in cold water, to remove all possible juices and soluble matter. The grayish-white fibrous mass thus obtained had practically no odor or taste. When some of it was boiled in water, however, it developed a definite meaty flavor; a trace in five minutes, considerable in thirty-five minutes, and the maximum intensity in three and one-half hours. This flavor was found to consist mostly of odor and very little of taste and to be due to a mixture of substances including hydrogen sulfide and several acids and amines.

Some expressed juice from raw meat was found to have a weak blood-like odor and taste. On heating, albuminous matter coagulated but no meaty flavor developed. Thus it was suggested that the flavor of raw meat resides in the juice whereas that of cooked meat is produced by the action of heat on the fiber.

RECOMMENDED DAILY DIETARY ALLOWANCES*

REVISED, 1948

Food and Nutrition Board, National Research Council, Washington, D. C.

	Calories[1]	Protein	Calcium	Iron	Vitamin A[2]	Thiamine[3]	Riboflavin[3]	Niacin (nicotinic acid)[3]	Ascorbic acid)	Vitamin D
		grams	*grams*	*mg.*	I.U.	*mg.*	*mg.*	*mg.*	*mg.*	I.U.
Man (154 lb., 70 kg.)										
Sedentary	*2400*	70	*1.0*	12[4]	5000	1.2	*1.8*	12	75	[5]
Physically active	3000	70	*1.0*	12[4]	5000	1.5	*1.8*	15	75	[5]
With heavy work	4500	70	*1.0*	12[4]	5000	*1.8*	*1.8*	*18*	75	[5]
Woman (123 lb., 56 kg.)										
Sedentary	*2000*	60	*1.0*	12	5000	*1.0*	1.5	*10*	70	[5]
Moderately active	*2400*	60	*1.0*	12	5000	1.2	*1.5*	12	70	[5]
Very active	3000	60	*1.0*	12	5000	1.5	*1.5*	15	70	[5]
Pregnancy (latter half)	*2400*[6]	85	1.5	15	6000	*1.5*	2.5	*15*	100	*400*
Lactation	3000	100	2.0	15	8000	*1.5*	3.0	*15*	150	*400*
Children up to 12 yrs.[7]										
Under 1 yr.[8]	*110*/2.2 lb. (1 kg.)	3.5/2.2 lb. (1 kg.)	1.0	6	1500	0.4	0.6	4	30	*400*
1–3 yrs. (27 lb., 12 kg.)	1200	40	1.0	7	2000	0.6	0.9	6	35	400
4–6 yrs. (42 lb., 19 kg.)	1600	50	1.0	8	2500	0.8	1.2	8	50	400
7–9 yrs. (58 lb., 26 kg.)	2000	60	1.0	10	3500	1.0	1.5	10	60	400
10–12 yrs. (78 lb., 35 kg.)	2500	70	1.2	12	4500	1.2	1.8	12	75	400
Children over 12 yrs.[7]										
Girls, 13–15 yrs. (108 lb., 49 kg.)	2600	80	1.3	15	5000	1.3	2.0	13	80	400
16–20 yrs. (122 lb., 55 kg.)	2400	75	1.0	15	5000	1.2	1.8	12	80	400
Boys, 13–15 yrs. (108 lb., 49 kg.)	3200	85	1.4	15	5000	1.5	2.0	15	90	400
16–20 yrs. (141 lb., 64 kg.)	3800	100	1.4	15	6000	*1.7*	2.5	*17*	100	400

Note. Italicized figures represent changes from the 1945, Revised, Recommended Dietary Allowances.

* Objectives toward which to aim in planning practical dietaries: The recommended allowances can be attained with a good variety of common foods which will also provide other minerals and vitamins for which requirements are less well known.

[1] Calorie allowances must be adjusted up or down to meet specific needs. The calorie values in the table are therefore not applicable to all individuals but rather represent group averages. The proper calorie allowance is that which over an extended period will maintain body weight or rate of growth at the level most conducive to well-being.

[2] The allowance depends on the relative amounts of vitamin A and carotene. The allowances of the table are based on the premise that approximately two-thirds of the vitamin A value of the average diet in this country is contributed by carotene and that carotene has half or less than half the value of vitamin A.

[3] For adults (except pregnant and lactating women) receiving diets supplying 2000 calories or less, such as reducing diets, the allowances of thiamine and niacin may be 1 mg. and 10 mg. respectively. The fact that figures are given for different calorie levels for thiamine and niacin does not imply that we can estimate the requirement of these factors within 500 calories, but they are added merely for simplicity of calculation. In the present revision, riboflavin allowances are based on body weight rather than caloric levels. Other members of the B complex also are required, though no values can be

given. Foods supplying adequate thiamine, riboflavin, and niacin will tend to supply sufficient of the remaining B vitamins.

[4] There is evidence that the male adult needs relatively little iron. The need will usually be provided for if the diet is satisfactory in other respects.

[5] The need for supplemental vitamin D by vigorous adults leading a normal life seems to be minimum. For persons working at night and for nuns and others whose habits shield them from the sunlight, as well as for elderly persons, the ingestion of small amounts of vitamin D is desirable.

[6] During the latter part of pregnancy the calorie allowance should increase approximately 20 percent above the preceding level. The value of 2400 calories represents the allowance for pregnant, sedentary women.

[7] Allowances for children are based on the needs for the middle year in each group (as 2, 5, 8, etc.) and are for moderate activity and for average weight at the middle year of the age group.

[8] Needs for infants increase from month to month with size and activity. The amounts given are for approximately 6 to 8 months. The dietary requirements for some of the nutrients such as protein and calcium are less if derived largely from human milk.

Further recommendations:

Fat. There is available little information concerning the human requirement for fat. Fat allowances must be based at present more on food habits than on physiological requirements. While a requirement for certain unsaturated fatty acids (the linoleic and arachidonic acids of natural fats) has been amply demonstrated with experimental animals, the human need for these same fatty acids is not known. In spite of the paucity of information on this subject there are several factors which make it desirable (1) that fat be included in the diet to the extent of at least 20 to 25 percent of the total calories and (2) that the fat intake include essential unsaturated fatty acids to the extent of at least 1 percent of the total calories. At higher levels of caloric expenditure, e.g., for a very active person consuming 4500 calories and for children and for adolescent persons, it is desirable that 30 to 35 percent of the total calories be derived from fat. Since foodstuffs such as meat, milk, cheese, nuts, etc., contribute fat to the diet, it is necessary to use separated or "visible" fats such as butter, oleomargarine, lard, or shortenings only to supply one-third to one-half the amounts indicated.

Water. A suitable allowance of water for adults is 2.5 liters daily in most instances. An ordinary standard for diverse persons is one milliliter for each calorie of food. Most of this quantity is contained in prepared foods. At work or in hot weather, requirements may reach 5 to 13 liters daily. Water should be allowed *ad libitum*, since sensations of thirst usually serve as adequate guides to intake except for infants and sick persons.

Salt. The needs for salt and for water are closely interrelated. A liberal allowance of sodium chloride for the adult is 5 grams daily, except for some persons who sweat profusely. The average normal intake of salt is 10 to 15 grams daily, an amount which meets the salt requirements for a water intake up to 4 liters daily. When sweating is excessive, one additional gram of salt should be consumed for each liter of water in excess of 4 liters daily. With heavy work or in hot climates 20 to 30 grams daily may be consumed with meals and in drinking water. Even then, most persons do not need more salt than usually occurs in prepared foods. It has been shown that after acclimatization persons produce sweat that contains only about 0.5 gram to the liter in contrast with a content of 2 to 3 grams for sweat of the unacclimatized person. Consequently after acclimatization, need for increase of salt beyond that of ordinary food disappears.

Iodine. The requirement for iodine is small, probably about 0.002 to 0.004 mg. daily for each kilogram of body weight, or a total of 0.15 to 0.30 mg. daily for the adult. This need is met by the regular use of iodized salt; its use is especially important in *adolescence* and *pregnancy*.

Phosphorus. Available evidence indicates that the phosphorus allowances should be at least equal to those for calcium in the diets of children and of women during the latter part of pregnancy and during lactation. In the case of other adults the phosphorus allowances should be approximately 1.5 times those for calcium. In general it is safe to assume that if the calcium and protein needs are met through common foods, the phosphorus requirement also will be covered, because the common foods richest in calcium and protein are also the best sources of phosphorus.

Copper. The requirement for copper for adults is about 1 to 2 mg. daily. Infants and children require approximately 0.05 mg. for each kilogram of body weight. The requirement for copper is approximately one-tenth that for iron. A good diet normally will supply sufficient copper.

Vitamin K. The requirement for vitamin K usually is satisfied by any good diet except for the infant in utero and for the first few days after birth. Supplemental vitamin K is recommended during the last month of pregnancy. When it has not been given in this manner, it is recommended for the mother preceding delivery or for the baby immediately after birth.

Folic acid. Evidence for recognizing folic acid (pteroylglutamic acid, vitamin B_c, L. casei factor or vitamin M) as an essential human nutrient is presented in the text. The quantitative requirement cannot be closely estimated from evidence now available.

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